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Old and New Pathways in Human Genetics[1]

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THE year 1950 rounds out the first half-century of the modern science of genetics. During these fifty years this branch of biological science has grown and developed until it, too, has its own branches and subdivisions. Meanwhile, lines of demarcation originally existing between genetics and other sciences have gradually disintegrated until now genetics merges imperceptibly into many other fields. Agricultural genetics, physiological genetics, developmental genetics, biochemical genetics, radiation genetics, cytogenetics, population genetics, and human and medical genetics have all emerged as coordinated fields of research, and each has made notable contributions to knowledge and to human welfare.

Although speculations on matters of heredity may be found far back in human history, and although the pioneer researches of Mendel are now nearly one hundred years old, modern genetics dates only from the turn of the century. When Mendel's principles had been rediscovered and had been tested on various experimental organisms, when the cytological basis for the phenomena had been recognized, and when the earlier basic principles had been expanded, extended, and woven into an understandable pattern, it was inevitable that an attempt should have been made to determine the applicability of these principles to man.

During the first decade of the century the literature on human genetics began to appear under such names as Ballowitz, Bulloch, Davenport, Drinkwater, Farabee, Fischer, Folkar, Galton, Garrod, Gossage, Guthrie, Guyer, Harmon, Holmes, Hurst, Nettleship, Pearson, Vogt, Weinberg and Wilson. During this decade there was begun the publication of the valuable *Treasury of Human Inheritance* under the editorship of Karl Pearson. While some of the studies had a strong eugenics slant, others dealt with human genetics *per se*.

It quickly became apparent that Mendel's principles were indeed applicable to man, and the discovery of new and more complicated principles through the years has served only to strengthen and further document the conclusion that the genetics of man is essentially like that of other organisms. Virtually

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every basic law and principle of modern genetics can be illustrated with human material, and some of these principles have in fact been derived from data on man.

In spite of the flurry of interest in human heredity during the first decade or two of the century, this interest, particularly in America, was short lived. The rise of the experimental method in genetics with its prospect of definitive results within reasonable time limits caused many geneticists starting out on their careers to feel a hesitancy towards forsaking experimental work, and to fear that they might be embarking on non-scientific procedures in taking up the study of human heredity. As a result, the programs of the Genetics Society of America for the ten years following its inception carried a scant dozen papers on the genetics of man.

On the last day of the year 1941 there was held at the Dallas meetings of the A.A.A.S. a symposium on human genetics, jointly sponsored by the American Society of Naturalists, the Genetics Society of America, the American Society of Zoologists, and the Botanical Society of America. Following this symposium, interest in the study of human heredity in America gradually increased. The old Eugenics Record Office at Cold Spring Harbor, which had faded from the picture in the face of a growing skepticism regarding the eugenics movement on the part of many geneticists, was replaced in this country by such centers of research in human genetics as the Ohio State University, the University of Michigan, the Bowman Gray School of Medicine, the University of Minnesota, the University of Chicago, the New York City Examiner's Office, and the New York State Psychiatric Institute. Other centers are developing rapidly. The culmination of these activities in America was the formation of the American Society of Human Genetics in 1948, an event which holds promise of a true flowering of the subject on this side of the Atlantic.

Meanwhile various European laboratories had been far-sighted enough to perceive the importance of the study of human heredity, and centers of activity there had grown apace. Those in Germany and Russia were unfortunately detoured or terminated due to considerations of war or of conflicting ideologies, but those in England, Sweden and Denmark, and to some extent in Switzerland, Holland and other parts of Europe, are continuing to function at a high degree of efficiency. The recent formation by the International Union of Biological Sciences of a subsection on Human Genetics offers great hope that there may soon be a complete revival of international cooperation in the study of human heredity.

Within the last few decades remarkable progress has been made in the analysis of the genetics of man. The earlier studies dealt almost exclusively with individual families, and were concerned largely with conspicuous phenotypic discontinuities. If the trait were sufficiently striking and readily identified

data were often obtainable for several generations back. The families were of necessity selected, only those families containing at least one affected member being included in the studies. This, of course, created a bias in the data, but in spite of it many anomalies and diatheses were shown to have genetic bases, and for some of them presumptive evidence was obtained for specific types of hereditary behavior.

The discovery of the human blood groups by Landsteiner and the remarkable extensions of the original discovery by Levine, Wiener, Hirszfeld, Bernstein, Race and others opened the way to an entirely new approach to human genetics: the population approach. The blood groups have been to human genetics what Drosophila has been to classical genetics. The first of the many important contributions which the study of blood groups made to the field of human heredity was the providing of "test characters" for analysis. Test characters are normal traits which can easily and accurately be ascertained, which are dependent upon a single pair or set of alleles, which are relatively uninfluenced by nongenetic impacts, and in which both or all alleles of the set are present in the population with reasonable frequencies.

In the study of test characters, the data are collected wholly at random, that is, without regard to the phenotypes of the individuals. The data may represent only individuals in the population, without regard to genetic relationship, or they may be in the form of families or kinships. Both kinds of data are valuable, each in its own way. When families are investigated in this manner, it is with the assurance that the majority of them will exhibit intrafamilial variation. The many blood agglutinogens are of this nature, as is the taste deficiency to phenyl-thio-carbamide (12, 65).

Test characters present the student of human heredity with problems not encountered by the laboratory geneticist. In the laboratory or field plot, where selection and inbreeding may be freely practiced, relatively isogenic, true-breeding lines may be established. From such lines we may, by controlled matings, obtain classical genetic ratios, and thus determine the mode of inheritance involved in any specific trait, and the genotypes of particular individuals, with relative ease.

In man, however, we must work with highly heterozygous material which is frequently restricted to two generations, and sometimes to but one, and in which the genotypes are in many cases capable only of incomplete specification. Under these circumstances even well-classified data will often contain mixtures of genotypically different types of matings.

The approach to the solution of such problems constitutes one of the most important milestones in the history of human genetics. In 1925 Bernstein, by means of cleverly designed extensions of the Hardy-Weinberg law of equilibrium, showed that data on test characters are subject to rigorous mathematical analysis on the basis of the frequencies of the postulated genes in the

population. The immediate outcome of Bernstein's studies was his proof that the ABO blood groups are inherited on the basis of a set of triple alleles, and not, as had previously been thought, on the basis of two pairs of genes. The long range outcome of these studies, however, has been the development of population genetics as an important area of research.

Gene frequency analyses for many types of transmission in populations were rapidly developed by Cotterman, Haldane, Lenz, Hogben, Snyder, Wellisch, Wiener and others. To such an extent have these methods developed that, as Cotterman has pointed out, unit factor inheritance may be detected in data comprising but a single generation, that is, in sibships of completely unspecified parentage. Thus in the course of the development of methods for analyzing the genetics of man, the required number of generations has been reduced first to two, and finally to but one, while the requisite knowledge of parental genotypes has been gradually reduced and finally eliminated altogether.

It must not be thought that methods which lessen the required number of generations or which minimize knowledge of parental genotypes are as desirable or efficient as classical methods. Such methods merely serve, as efficiently as possible, in an area in which test matings with precisely known genotypes are not available.

It is obvious that the methods of population genetics are not applicable to single families, and will not automatically correct the bias resulting from the selection of families on the basis of the inclusion of at least one affected member. Haldane, Hogben and others, however, have provided correction factors for cases of this sort, and such instances may now be analyzed efficiently.

Meanwhile a determined effort was being made to study linkage in man, and to map the human chromosomes. Here further new problems presented themselves. It was soon apparent that in dealing with human material, just as a single phenotype will often include two indistinguishable genotypes, so a single heterozygous genotype will include two indistinguishable phases, coupling and repulsion. This seemingly insurmountable difficulty was solved with increasing degrees of efficiency by Bernstein, Wiener, Haldane, Fisher, Penrose, and finally by Finney. The mathematical methods used are monuments to the ingenuity and ability of biometricians, and have helped to repay the debt which human genetics owes to other sciences. By the use of such methods a start has been made on the mapping of human chromosomes (71).

The original methods devised for studying the dynamics of gene frequencies were based on the assumption of infinitely large populations in equilibrium. But man is a gregarious animal, and tends to cluster in groups of limited size. Within restricted populations sampling fluctuations, which constitute a characteristic of the genetic mechanism as inherent as any of its other properties, may have rather surprising effects.

Natural populations which at first sight may appear to be very extensive

are in fact often composed of numerous local and more-or-less self-contained breeding units (isolates). In a completely self-contained unit, the gene frequency dynamics will be determined by the size and mating pattern of the unit. Where some intermigration occurs, the evolution of the over-all population will depend in important ways on the numbers in the individual subgroups and on the extent of the intermigration. Among the hundreds of millions of human beings whose distribution is practically continuous over the earth's surface there are countless isolated rural groups which contribute only occasional migrants to other populations. Even in urban areas isolates occur on the basis of social class, religious affiliations, culture patterns and other isolating mechanisms. The mating patterns of mankind are in fact those imposed by the occurrence of many partial isolates. Dahlberg has roughly estimated from the frequencies of various types of consanguineous marriages that the average effective mating number of such quasi-isolates in Europe lies somewhere between 400 and 3000, and this figure may be taken as applicable to America also. In earlier centuries the numbers must have been even smaller.

Considerations such as these lead to important conclusions regarding human genetics. While sampling fluctuations would be likely to result only in negligible shifts in gene frequencies from generation to generation in large populations, they may in small populations of a few hundred or less bring about radical alterations in gene frequencies quite aside from mutation or selection.

It happens, moreover, that the sampling fluctuations tend to be cumulative in their effects. Since the sample of genes drawn from the supply of any generation must in turn generate the supply from which a new sample will be drawn when the progeny reproduce, the allele which is less frequent in the parental generation tends to have its frequency further reduced in progeny resulting from samples drawn from the supply. Such cumulative changes result in what is known as genetic drift. It can lead to the spread of a new mutant gene through a small population, or, more often, to the loss of a new allele before it has had a chance to spread appreciably or at all.

The human geneticist today must therefore describe variability in two categories: that of the individual and his kinship, and that of the population. The individual and the members of his family are to be described in terms of *Mendelian genetics;* that is, in terms of the presence or absence of specific alleles, plus, of course, the results of environmental circumstances. The population, on the other hand, is to be characterized in terms of *population genetics;* that is, in terms of the relative proportions of various alleles, and of the over-all environmental impacts.

Among the basic principles of population genetics which are essential to the working materials of the modern student of human heredity are the following ('69):

1. Classical Mendelian ratios are not to be expected in random samples

drawn from a population, nor even necessarily from classified data including the pooled offspring from phenotypically similar matings. Classical ratios are to be found only among the offspring of an individual family if there are sufficient children, or among the pooled offspring of a series of families where the parental mating type of each family is in fact genotypically identical with that of every other family. Since the genotypes of human beings are seldom capable of specification, even the best classified data will usually contain mixtures of genotypes and must not be expected to yield Mendelian ratios.

2. In spite of the absence of classical ratios, predictable ratios of another sort do occur under the conditions stated above. These ratios are population ratios, and are expressed in terms of the proportions of the alleles. They are dynamic ratios in contrast to static Mendelian ratios. Among random matings of individuals exhibiting a trait due to a dominant gene, for example, there will be some in which one or both parents are homozygous, resulting in the Mendelian ratio of dominants to recessives of 1:0, and others in which both parents are heterozygous, resulting in the Mendelian ratio of $\frac{3}{4}:\frac{1}{4}$. In a random-mating population these static ratios are jointly expressed as one dynamic population ratio, $[(1 + 2\,q)/(1 + q)^2]:[q^2/(1 + q)^2]$ where q is the proportion of the recessive allele in the population (66). Many similar population ratios have been derived and are of the utmost value in the analysis of human genetics.

3. The comparison of predicted and observed population ratios can be used to estimate the number and kind of genes responsible for a hereditary variation in a population just as the comparison of predicted and observed Mendelian ratios can be used to estimate the number and kind of genes involved in a laboratory experiment. Goodness of fit tests have been formulated for many such estimations.

4. The inherent characteristics of the Mendelian mechanism are such that in a large population in which the effects of mutation, selection, and in-and-out migration are either negligible or balancing each other, the proportions of the various genes will remain constant from generation to generation, regardless of the dominance or recessivity of each gene. If there is in addition random mating in a constant environment, the proportions of the genotypes, and thus of the traits produced by them, will likewise remain constant.

5. Changes in the proportionate occurrence of genes or traits can be brought about, however, by various phenomena including mutation, selection, inbreeding, assortative mating, migration and, particularly in isolates, genetic drift. The rates and extents of such changes are capable of mathematical estimation. The methods have been summarized in recent books by Dahlberg, Hogben, Li and others.

6. The occurrence of genetic linkage between the genes for two traits does not change the association between those traits in the population from what it

would be if they were not linked. Stated conversely, a correlation between two traits in a free-breeding population does not indicate genetic linkage between the genes responsible for the traits.

7. The inherent characteristics of the linkage mechanism are such, however, that the occurrence of linkage may be detected without recourse to the classical distinctions between coupling and repulsion phases, by means of specially constructed methods applicable to human material.

Unfortunately theoretical considerations of population genetics are far in advance of empirical investigations. There is as yet insufficient realization of the necessity of carefully collected field data on the genetics of human populations. The realization is growing, however, and is even beginning to invade the related fields of anthropology and medicine. The recent Cold Spring Harbor symposium on the origin and evolution of man brought together anthropologists, physicians, and geneticists, and has done much to point the way to cooperative field efforts.

Even with the limited population data now available, however, one clear conclusion seems to be emerging (69, 70). Human populations differ one from the other almost entirely in the varying *proportions* of the allelic genes of the various sets of hereditary factors, and not in the *kinds* of genes they contain. The extreme positions held by those who on the one hand maintain that there are no significant genetic differences between human races, and those who on the other hand hold that certain races are "superior" and others "inferior", require drastic modification in the light of the accumulated data on the gene frequency dynamics of human populations.

Throughout the growth and development of human genetics there have been other mistaken beliefs to be corrected. One of the earliest and farthest-reaching fallacies in the philosophical approach to human problems was the belief that if a genetic basis were demonstrated for a certain trait, that trait could not be subject to enviromental modification; and conversely, if a trait were shown to be influenced by the environment, it could not at the same time be genetically determined. Although many of us have for years called attention to this fallacy, it still crops up in the literature, especially that of medicine, sociology, psychology, and education.

There is usually an element of fear present in the case of the heredity-environment fallacy. For the physician, there may be a certain reluctance to accept the genetic basis for a disease or anomaly on the grounds that it would thereby be useless to attempt therapy. For the sociologist or psychologist, the reluctance involves the fear that new or changed attitudes could not be brought about if there were any genetic basis for the original development of individual differences in behavior. The fallacy appears in subtle ways and is not always easy to detect. In a recent book on Intergroup Relation Centers (9), the author states that hostilities and methods of expressing animosities are not born in children,

and therefore they can be controlled (italics mine). It may indeed be true that such things are not born in children, but even if they were, this would not determine that they could not be controlled.

The same author states that science proves that differences in knowledge, customs, and personality are not transmitted biologically. Science proves no such thing. There is little significant scientific evidence either way on the possible genetic basis for personality, but there is a patent fear, on the part of the author of the statement, that if there were such a basis, intergroup relations centers might lose their usefulness.

Two psychologists who recently maintained that massive doses of vitamin A would cure colorblindness wrongly concluded from their studies that it is "obvious that red-green colorblindness is not the simple Mendelian trait that popular theories assume it to be" (18). When the results were attacked by another psychologist (50), this worker upheld the postulate that "certain anomalies of color vision are both hereditary *and incurable*" (italics mine), thus using the same misconceived argument, but the other way around.

We must keep constantly in mind the fact that each person with all his characteristics is the cooperative result of genetic and environmental agencies. The genes and their accompanying cytoplasm do not alone make a man or woman. There is always an environment in which the individual develops, although the relative effects of differences in gene substitutions and differences in environmental forces will vary from trait to trait.

There are human genes, such as those responsible for the blood antigens, which express themselves rather uniformly within any known range of environment. There are other genes, such as those for resistance and susceptibility, the expression of which may vary considerably in different environments. It is probable that, in general, the fewer biochemical steps that intervene between a gene and its resulting trait, the less significantly will it be environmentally influenced, and the closer will be the correspondence between the presence of the gene and the presence of the trait.

It is important to make the distinction between what the gene actually does, which is apparently of a biochemical nature such as antigenic or enzymatic activity, and what the end result may be, under extragenic influences. This point of view is especially important when it is realized that the environmental events intervening between gene actions and finished characters in man may range from such overt occurrences as trauma and infection to the most subtle embryological, immunological and psychological phenomena. Furthermore, there is no reason to doubt the feasibility, and in many cases the desirability, of attempting the control of such environmental agents. The recognition of a genetic potential in many traits should serve only to broaden rather than to narrow the scope of activity of the physician, the psychologist, the sociologist, and the educator.

Moreover, the recognition of the dual action of genetic and environmental agencies in the production of finished characters makes it possible to frame the questions as to how much of the variability in a given trait in a specified population in a specified environment is due to differences in the genotypes of the individuals concerned, and how much is due to variations in the environment under discussion. The mere collection and analysis of families will offer little information on these points. Similarity or variability within families may conceivably be due as well to non-genetic agencies as to genetic factors. In addition to pedigree studies we must use methods designed to discriminate between the potential causes of the variation. Such methods involve the observation of a series of genetically diverse individuals in the same environment, and of genetically similar individuals in diverse environments.

The twin studies by such investigators as von Verschuer, Newman, Rife, and Kallmann are examples of this type of procedure. So also are the institutional and foster home studies of students such as Burks, Freeman, and Leahy. Investigations of this nature mark the beginnings of an attempt to analyze traits other than those dependent on single gene substitutions.

It was logical that the earlier studies and even the first of the new methods devised for analyzing human genetics should concern themselves with single gene effects. Such effects are often striking, easily recognizable, and are usually sharply discontinuous. They are found to occur in practically every structure, organ and tissue of the body, and in nearly all physiological processes. We now have presumptive evidence that more than 100 variations (mostly pathologic) in the skin and its derivatives, more than 100 eye abnormalities, and a comparable number of skeletal anomalies are attributable to single gene substitutions. There is reasonable evidence of single gene determination for a score of blood dyscrasias and for comparable numbers of aberrations of the muscular system, of nervous disorders, and of metabolic and endocrine disturbances.

On the other hand, there are remarkably few non-pathological variations in man which have been demonstrated to be the results of single gene substitutions. The blood group antigens, the taste ability and deficiency for phenyl-thiocarbamide, the direction of the fine hair of the forehead and one or two others represent a major portion of normal human characters affected by known single genes. Recent studies by Spuhler, Reed, Rife, and others offer some hope that this list may be augmented.

At any rate our precise knowledge of human genetics is largely confined to the effects of single gene substitutions. Among other known facts about such characters is the discovery that they can be simulated by the effects of appropriate environmental agencies in the absence of the gene. The resulting "phenocopies" are often indistinguishable from the effects of the genes themselves. In human material, certain conditions apparently occur as single-gene effects in some families and as phenocopies in others; for example, the skeletal and

neurological anomalies following irradiation (49), the eye defects as sequellae to infection such as rubella (28), and the simulated heart troubles brought on by environmentally conditioned anxiety reactions (70).

Finally it has been shown that the effect of a gene substitution at any locus may be influenced by the genes at many other loci, and that conversely most single genes have multiple effects, often on viability, in addition to some major action.

It is tempting, in the face of the striking and variable effects of single-gene substitutions, to suppose that collectively they play a major role in human genetics. It is becoming more and more apparent, however, that single-gene differences resulting in marked phenotypic discontinuities are not in fact the most common type of genetic variability. Among the effects of radiation on gene mutation, for example, are some conspicuous phenotypic effects apparently identical with spontaneous mutations; a larger number of lethal mutations; and the largest number, by far, of mutations, the only discernible effects of which are slight changes in viability, vigor, or other physiological activities. Natural mutations appear to be distributed over a similar spectrum.

Probably both morphological and physiological characters affect viability, and there seems to be a general parallelism between the conspicuousness of the visible effect of a gene and the degree of viability impairment which results. Broadly speaking, the more striking the effect, the greater is the reduction in viability. Thus the largest class of mutant genes is composed of those genes which individually do not have readily discernible phenotypic effects, but for which the cumulative effects may be quite demonstrable.

Although most of the characteristics in man which have been adequately analyzed from the genetic standpoint are pathological discontinuities, the significant differences between individuals and between populations are to be found in such things as intelligence, special abilities, social behavior, size and features. These are traits of a non-pathological nature; moreover, they follow a continuous distribution rather than a discontinuous one. Insofar as they have a genetic basis, therefore, they must depend upon multifactorial heredity involving cumulative effects of genes.

The importance of the problems of dealing with such cumulatively acting genes has so impressed Mather and his colleagues that they have designated genes of this sort *polygenes*. It is assumed that the effect of an individual gene of a polygenic series approaches the limit at which it can not be distinquished from an environmental increment. In contrast, the single genes responsible for conspicuous phenotypic discontinuities are called *major genes*. It is possible to identify the latter individually, and to assign them to precise loci and specific linkage groups.

Polygenes, on the other hand, can not be individually so identified and so localized. Their effects appear to be quantitatively equivalent and cumulative.

Their existence must be accepted, however, if for no other reason than the effectiveness of selective breeding for almost any continuously variable quantitative character in a genetically heterogeneous population. There is, moreover, evidence that polygenes, like classical major genes, undergo segregation and crossing over.

If then, as seems clear, genes with individually minute but cumulatively appreciable effects constitute the largest class of available mutant genes, much of the genetic variability of man is contingent upon multifactorial inheritance. Not only most of the genetic variability, but most of the resulting phenotypic variability as well, must depend upon such genes, since natural selection tends to keep at low incidences the large discontinuities produced by major genes, because of the viability impairment connected with them.

Almost the only discernible single-gene differences which are found at appreciably high frequencies in human populations are those which appear to be approximately neutral in their viability effects. The genes concerned are those for the blood group antigens, taste deficiency, color vision, hair whorl, and similar neutral factors. The genes for thalassemia and for sickle cell anemia which have recently been so carefully studied by Neel, present exceptions for which we do not at present have a clear explanation. In these instances a relatively high frequency of the traits has been maintained in the face of the elimination or decreased fertility of the affected homozygotes. Whether an inordinately high mutation rate, a selective advantage of the heterozygote, or some other explanation, will be found to apply, only time will tell. Recent evidence from Reed's laboratory (61) that fibrosis of the pancreas presents a similar situation raises the possibility that mutation rates in man may prove to be higher than has been realized. Nevertheless, of the hundreds of severe abnormalities in man which may be attributable to single-gene substitutions, only a few have population incidences above one in ten thousand, and the vast majority have very much lower occurrences than this.

In a recent discussion of these problems, David and I (15) suggested that if two unrelated people were picked at random from a population, or even one from each of two populations, they might be found to differ in respect to one or another of the blood antigens, and one might be a taster of phenyl-thio-carbamide and the other a non-taster. Beyond this it is highly probable that few if any of the observable phenotypic differences between them would be referable to known major genes. And yet we know at least the physical differences to be largely genetic because of the almost complete physical identity of the members of any pair of monozygotic twins.

It follows that the major part of such genetic differences as are involved in the non-pathological range of human variability is most probably multifactorial in nature. Recognition of this fact may set limits to the amount of information

which we may expect to gain through continued analysis of single-gene differences.

I would be the last one to suggest that we should cease searching for and describing individual gene effects. It is essential that we continue to develop and refine the methods for detecting and analyzing the activities of major genes in human populations. Such analyses provide, among other things, as I shall shortly describe, valuable practical applications in medicine.

But, as David and I have recently pointed out, if human genetics is to progress along fresh pathways, the traditional atomistic approach must be supplemented by new methods which will provide information on multifactorial inheritance. We must be able to analyze genetic variability without recourse to classical single-gene analyses. The newer types of twin and twin-family studies appear to be a fruitful approach for this kind of investigation. Although the technics need elaboration and refinement, much progress is being made through quantitative comparisons of intra-pair differences in monozygotic and dizygotic twins separated and together, twin-family analyses, and the use of co-twin controls.

If the anthropologist, the psychologist, the sociologist, and the geneticist are to join forces in the genetic analysis of racial traits which are significant on the level of intelligence, personality, and social behavior, the implications of multifactorial inheritance must be carefully studied. Such transmission would seem, for example, less likely to bring about phenotypic differentiation through genetic drift than would the transmission of major genes, since the effects of individual multifactorial genes are apparently in large part mutually interchangeable. Even though genetic drift should result in the accumulation of different constellations of such genes in various populations, the overall phenotypic manifestations would tend to remain constant, since the relative proportions of plus and minus genes should be about the same from one population to the next. Even in occasional instances where genetic drift does lead to phenotypic differentiation between small populations, this would have little chance of persisting after the populations expanded, unless it had a high adaptive value. As Dolzhansky and Montagu have pointed out, flexibility and plasticity of behavioral adjustments are likely to have had selective advantages over fixed or stereotyped responses in human intelligence and social behavior.

I can not close this discussion without some reference to the important advantages to the health and welfare of mankind which have accrued from our increasing knowledge of human genetics. In past years those persons who have been concerned with the progress of medicine have given their chief attention to the problems of the alleviation and control of unfavorable and deleterious agencies of the environment. Throughout the decades increasing degrees of mastery have been achieved over the harmful and debilitating effects of infectious agents, malnutrition, trauma, emotional stress, and occupational hazards.

These achievements properly stand as significant monuments to the abilities, energies, and enthusiasms of those who have accomplished so much for medicine and human welfare.

The decisive roles played by the bacteriologist in facilitating the control of infectious disease, by the biochemist in outlining the regulation of nutritional disorders, by the psychologist and psychiatrist in aiding in overcoming the harmful effects of emotional stresses, by the physician in combating the ravages of physiological aberrancies, and by the surgeon in repairing damage due to trauma and irritation, are now being paralleled by the medical geneticist, who is making possible the understanding and control of genetic disease.

The pioneering studies of such investigators as Macklin, Lenz, Roberts, and Allan have led to a wide-spread attack on the problems of medical genetics, and have resulted in a series of practical applications. Those applications include the clinical detection of genetic carriers of disease (51), the earlier and more accurate identification of morbific genetic entities (46), the instituting of therapeutic and preventive measures based on such detection and identification (68), the developing of genetic prognoses (67), and the solution of immunological problems such as hemolytic disease of the newborn (43), and of medicolegal problems such as the determination of disputed paternity (77).

Rapid progress is being made along all these lines, and it would be impossible to present details here concerning any of them. The increase in sound genetic information in the newer medical text books and the growing number of courses in medical genetics in medical schools, however, testify to the appreciation of the genetic viewpoint by the physician.

To the medical members of the society I would bring a reminder that, as Macklin has so clearly stated, when it is realized that the very early signs of a disease, so often at present unrecognized, are to be found more frequently in the relatives of a patient with an overt condition than anywhere else, these early signs will be actively searched for. Slight but significant deviations from normality, which have in the past been ignored by physician and patient alike, will take on new and important meanings in the light of genetics, giving rise to new criteria for diagnosis, earlier identification, and consequent new opportunities for prevention and therapy.

Furthermore, the detection of genetic carriers will make possible a sharpened approach to the physiology and biochemistry of disease, by providing for study a relatively large number of people in the very early stages of the conditions.

The physician is in a strategic position to obtain critical genetic data for prognoses. It is especially important that physicians should record *consecutive* series of family histories on various anomalies as the patients appear in the office, regardless of whether there is a patent familial occurrence in every case. Too often only those families are recorded and reported in which several members exhibit the disease, while the sporadic cases are not considered worthy of

publication. Yet these are the very data which make accurate genetic prognosis possible.

To both the medical and anthropological members of the society I would point out that empirical data have not nearly caught up with theoretical considerations of human genetics. We need accurate data on the frequencies of all sorts of characteristics in populations, on their distributions within families, on the physiological and biochemical activities of the genes responsible for them, on the formation of isolates within larger populations, and on the extent of inbreeding and assortative mating within such isolates and of intermigration between them. The recent reports of Böök, Boyd, Kemp, Mourant, and Penrose are excellent examples of what can be done along these lines.

The human genetic studies of the future must be cooperative efforts. Only by teamwork involving scientists from many areas can the understanding of the genetics of man be expected to advance appreciably. To those of you in related fields who are willing to lend your aid and advice to such teams, it may be confidently promised that in direct proportion to the data and information thus provided there will emerge a deeper and more significant understanding of human biology, and recurrent new practical ways in which to use the information for the improvement of the health and welfare of all mankind.

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